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PREMIXED INSULIN REGIMEN TO BASAL-BOLUS INSULIN OUTCOMES IN TYPE 2 DIABETES SUBJECTS

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ABSTRACT

Background: PM (premixed) and BB (basal-bolus) insulin regimens have been compared in a number of trials in the literature, with differing outcomes. Additionally, there is a dearth of data in the Indian setting.

Aim: The purpose of this study was to evaluate the glycemic control and side effects of a premixed insulin regimen against basal-bolus insulin in individuals with type 2 diabetes mellitus in an Indian setting.

Techniques: In this study, 120 people with Type 2 diabetes mellitus who had had the disease for more than seven years were randomly assigned to two groups of sixty people each. Group I individuals were treated with BB, whereas Group II subjects were treated with an OM insulin regimen. At 4 and 12 weeks, hypoglycemic episodes and changes in glycemic parameters were evaluated.

Results: PM insulin significantly reduced FPG (fasting plasma glucose) from baseline at 4 weeks ($p=0.01$), while BB insulin only significantly reduced FPG after 12 weeks ($p<0.001$). At 4 and 12 weeks, the PM groups showed a greater decrease in FPG than the BB group ($p=0.03$ and 0.02 , respectively). Postprandial plasma glucose levels significantly decreased from baseline at 4 weeks ($p=0.03$ for both) and at 8 weeks ($p<0.0001$ for both). At four weeks, there was no intergroup difference ($p=0.14$). But in the PM group, it was significant at 12 weeks ($p=0.008$). The hypoglycemic event showed no discernible change ($p=0.47$).

Conclusion: The current study finds that both BB and PM insulin regimens significantly enhance glycemic control without putting their users at risk for severe hypoglycemia episodes. Therefore, insulin-related parameters like complexity and posology, as well as patient-related factors like dietary patterns and adherence levels, should influence the choice of insulin.

Keywords: basal-bolus insulin, Insulin naïve, glycated hemoglobin, hypoglycemia, premixed insulin

INTRODUCTION

Because type 2 diabetes mellitus (T2D) is progressive and chronic, insulin therapy is the gold standard for managing the condition in the majority of patients. The patient's eating habits, insulin therapy compliance, and expected adherence all play a major role in the choosing of insulin for diabetics. Additionally, it is controlled by a number of pre-existing OHAs (oral

hypoglycemic agents), drug interactions, and the intricacy of the regimen, all of which have a significant impact on the subjects' adherence to the insulin therapy.¹

In accordance with the 2022 American Association of Clinical Endocrinologists guidelines, the 2019 Research Society for the Study of Diabetes in India guidelines, and the 2017 International Diabetes Federation guidelines, While starting insulin therapy with either premix or basal insulin is advised, the Indian National Consensus Group (2013) suggests starting insulin therapy with premix only.² The Asian population subgroup with type 2 diabetes mellitus who have a HbA1c (glycated hemoglobin) level greater than 8.5% may require aggressive dual pharmacotherapy with prandial and basal insulin to control both post-prandial and fasting glucose levels, as basal insulin may not be enough to achieve glycemic control.³

Premixed insulin therapy, which consists of 70% intermediate-acting and 30% normal insulin, is sufficient for people who cannot monitor carbohydrates or who follow consistent food and lifestyle routines. The BB (basal-bolus) regimen mimics the pancreas' natural production of insulin.

It does, however, need regular and intentional self-monitoring. In comparison to Premix, basal bolus needs frequent dosing which can hurt patient adherence.⁴ The effectiveness of Pm and BB insulin regimens has been examined in the literature, with conflicting findings. While some studies suggest that both regimens are equally effective at decreasing HbA1c and controlling blood sugar, others demonstrate that one of the regimens is more effective. The incidence of hypoglycemia varies between PM and BB regimens, according to literature statistics. Nevertheless, there is a dearth of information about the Indian context in the literature.⁵ Therefore, the current study sought to compare the glycemic control and side effects of premixed insulin regimens to basal-bolus insulin in Indian insulin-naïve participants with type 2 diabetes mellitus.

MATERIALS AND METHODS

The purpose of the current prospective clinical observational study was to compare the glycemic control and side effects of premixed insulin regimens to basal-bolus insulin in insulin-naïve individuals with type 2 diabetes mellitus in an Indian setting. The Institute's Department of Medicine provided the study participants. Prior to their involvement in the study, all participants provided written and verbal informed consent.

Insulin-naïve individuals with type 2 diabetes mellitus who were between the ages of 18 and 65 and of both genders were included in the study. Subjects who were 18 years of age or older, had uncontrolled diabetes, uncontrolled lifestyle modification, three oral hypoglycemic drugs (as determined by the treating practitioner), and were willing to participate in the study met the inclusion criteria.

Subjects with a history of alcohol abuse, acute illness, serious concomitant diseases, comorbid chronic kidney or liver diseases, lactating or pregnant women, those taking medications that interfere with blood sugar levels, such as beta-blockers, thiazides, or steroids, and those who did not consent to participate in the study were all excluded from the study.

Blood pressure, hip circumference, weight, height, gender, and age were collected once study participants were finally included. BMI and the waist-hip ratio were also computed using this. As a measure of the effectiveness of either regimen, changes in HbA1c%, PPG, and FPG (fasting plasma glucose) were evaluated at 4 and 12 weeks. The American Diabetes Association and European Association for the Study of Diabetes classifications were used to identify hypoglycemia.^{6,7}

Level 1 hypoglycemia alert value is ≤ 70 mg/dL (3.9 mmol/L), which is low enough for fast-acting carbohydrate treatment and dose modification of glucose-lowering medication; level 2 clinically significant hypoglycemia is < 54 mg/dL (3.0 mmol/L), which is low enough to indicate serious, clinically significant hypoglycemia; level 3 severe hypoglycemia, which lacks a specific glucose threshold and is associated with severe cognitive impairment that requires outside help to recover. Standard care and treatment were provided to both groups. The majority of participants were taking a combination of metformin, glimepiride, and vildagliptin, which was kept constant throughout the research at the clinicians' discretion.

As directed by the attending clinicians, treatment was continued for pre-existing comorbidities, including dyslipidemia, hypertension, bronchial asthma, hypothyroidism, ischemic heart disease, and chronic obstructive pulmonary disease. Two injections of PM insulin were administered daily as part of the PM protocol. The BB regimen consisted of four injections per day, one dose of peakless insulin, and three doses of conventional insulin.

Using SPSS (Statistical Package for the Social Sciences) software version 24.0 (IBM Corp., Armonk, NY, USA), the collected data was statistically evaluated for descriptive measures, one-way ANOVA (analysis of variance), Pearson correlation, Kruskal-Wallis test, and chi-square test.

The mean, standard deviation, frequency, and percentages were used to express the results. A p-value of less than 0.05 was deemed statistically significant.

RESULTS

The goal of the current prospective clinical observational study was to compare the glycemic control and side effects of premixed insulin regimens with basal-bolus insulin in Indian insulin-naïve participants with type 2 diabetes mellitus. In the current study, 120 people with Type 2 diabetes mellitus who had had their condition for more than seven years were randomly assigned to two groups of sixty people each. Group I participants were treated with BB, whereas Group II participants received an OM insulin regimen. The study subjects in the BB and MP groups had mean ages of 54.41 ± 10.13 and 52.41 ± 8.58 years, respectively, which were not statistically significant ($p=0.43$).

Gender, type 2 diabetes mellitus, BMI, weight, dyslipidemia, hypertension, family history, and HbA1c did not significantly differ between the two groups ($p=0.32, 0.35, 0.37, 0.25, 0.75, 0.77, 0.97, 0.44$, and 0.13 , respectively). With $p=0.02$, the PM regimen showed a considerably greater reduction in postprandial glucose than the BB regimen (Table 1). In both BB and PM insulin regimens, PPG and FPG levels significantly decreased from baseline to 12 weeks. At 4 weeks, premix insulin significantly reduced baseline levels from 182.04 ± 49.28 to 146.6 ± 30.75 with $p=0.01$ and from 182.04 ± 49.28 to 131.4 ± 19.39 mg/dl with $p<0.0001$. FPG has been observed to drop with the BB regimen, from 191.41 ± 44.44 mg/dl at baseline to 141.24 ± 15.15 mg/dl at 12 weeks with $p<0.0001$.

Additionally, there was a substantial drop in FPG in the PM and BB groups at 4 weeks (146.78 ± 30.75 mg/dl and 167.78 ± 33.12 mg/dl, respectively; $p=0.03$) and 12 weeks (131.58 ± 19.39 mg/dl and 141.28 ± 15.59 mg/dl, respectively; $p=0.02$). From baseline to four weeks, PPG significantly decreased in the PM group (253.44 ± 54.28 mg/dl to 190.1 ± 32.45 mg/dl with $p=0.03$) and in the BB group (234.1 ± 66.18 mg/dl to 190.1 ± 22.45 mg/dl with $p=0.03$). At 12 weeks, the PM group experienced a decrease from 253.44 ± 54.28 mg/dl to 171.3 ± 16.60 mg/dl with $p<0.0001$, whereas the BB group experienced a decline from 234.1 ± 66.18 mg/dl to 158.5 ± 20.19 mg/dl with $p<0.0001$. Nevertheless, there was no intergroup difference in the PM group after 4 weeks (177.68 ± 24.22 mg/dl vs. 190.28 ± 32.45 mg/dl with $p=0.14$) or 12 weeks (158.68 ± 20.19 mg/dl and 171.48 ± 16.60 mg/dl with $p=0.008$).

HbA1c levels dropped from $8.36 \pm 1.06\%$ at baseline to $7.59 \pm 0.59\%$ at 12 weeks, a statistically significant shift with a percentage change of 9.16% ($p=0.0002$). The BB regimen individuals' mean HbA1c value changed from $7.88 \pm 0.76\%$ to $7.32 \pm 0.61\%$ between baseline and 12 weeks ($p=0.0007$), with a 7.06% percentage change. In comparison to the BB regimen, this demonstrated a superior and larger percentage reduction in HbA1c in the PM group. Nevertheless, the observed intergroup difference ($p=0.37$) was not statistically significant.

DISCUSSION

The current study included 120 individuals with Type 2 diabetes mellitus who had had the condition for more than seven years. They were divided into two groups of sixty individuals each, with Group II having an OM insulin regimen and Group I receiving BB therapy.

The study subjects in the BB and MP groups had mean ages of 54.41 ± 10.13 and 52.41 ± 8.58 years, respectively, which were not statistically significant ($p=0.43$). Gender, type 2 diabetes mellitus, BMI, weight, dyslipidemia, hypertension, family history, and HbA1c all showed statistically insignificant differences between the two groups ($p=0.32, 0.35, 0.37, 0.25, 0.75, 0.77, 0.97, 0.44$, and 0.13 , respectively). The PM regimen showed a considerably greater reduction in postprandial glucose than the BB regimen ($p=0.02$).

These demographics were similar to those of other research by Yavuz DG et al. (2015) and Anyanwagu U et al. (2017), in which the authors evaluated individuals with diabetes mellitus and similar demographics. In both BB and PM insulin regimens, it was shown that PPG and FPG levels significantly decreased from baseline to 12 weeks. At 4 weeks, premix insulin significantly reduced baseline levels from 182.04 ± 49.28 to 146.6 ± 30.75 with $p=0.01$ and from 182.04 ± 49.28 to 131.4 ± 19.39 mg/dl with $p<0.0001$. FPG has been reported to drop with the BB regimen from 191.41 ± 44.44 mg/dl at baseline to 141.24 ± 15.15 mg/dl at 12 weeks ($p<0.0001$).

Additionally, there was a substantial drop in FPG in the PM and BB groups at 4 weeks (146.78 ± 30.75 mg/dl and 167.78 ± 33.12 mg/dl, respectively; $p=0.03$) and 12 weeks (131.58 ± 19.39 mg/dl and 141.28 ± 15.59 mg/dl, respectively; $p=0.02$). These findings were in line with those of Testa MA et al. (2012) and Bai R et al. (2023), who likewise found that both BB and PM insulin regimens significantly decreased from baseline to 12 weeks in their respective trials. According to the study's findings, post-prandial glucose (PPG) significantly decreased from baseline to four weeks in the PM

group (253.44±54.28 mg/dl to 190.1±32.45 mg/dl with p=0.03) and in the BB group (234.1±66.18 mg/dl to 190.1±22.45 mg/dl with p=0.03).

At 12 weeks, the PM group showed a decrease from 253.44±54.28 mg/dl to 171.3±16.60 mg/dl with p<0.0001, whereas the BB group showed a decline from 234.1±66.18 mg/dl to 158.5±20.19 mg/dl with p<0.0001. Nevertheless, there was no intergroup difference in the PM group after 4 weeks (177.68±24.22 mg/dl vs. 190.28±32.45 mg/dl with p=0.14) or 12 weeks (158.68±20.19 mg/dl and 171.48±16.60 mg/dl with p=0.008). These results corroborated those of Miser WF et al. (2010) and Miyoshi H et al. (2021), whose authors reported significant PPG reduction with both PM and BB after three months.

The HbA1c results showed a statistically significant decrease from 8.36±1.06% at baseline to 7.59±0.59% at 12 weeks, with a percentage change of 9.16%. From baseline to 12 weeks, the mean HbA1c value in the BB regimen individuals changed from 7.88±0.76% to 7.32±0.61% (p=0.0007), with a 7.06% percentage change. In comparison to the BB regimen, this demonstrated a superior and higher percentage reduction in HbA1c in the PM group. Nevertheless, the observed intergroup difference (p=0.37) was not statistically significant.

These findings were consistent with those of Bellido V et al. (2015) and Ilag LL et al. (2007), whose authors likewise found significantly lower HbA1c values with both BB and PM groups.

CONCLUSIONS

Taking into account its limitations, the current study finds that both BB and PM insulin regimens significantly enhance glycemic control without putting their users at risk for severe hypoglycemia episodes. Therefore, insulin-related parameters like complexity and posology, as well as patient-related factors like dietary patterns and adherence levels, should influence the choice of insulin.

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S. No	Parameters	BB insulin (n=60)	PM regimen (n=60)	p-value
1.	Mean age (years)	54.41±10.13	52.41±8.58	0.43
2.	Gender			
a)	Males	36 (60)	26 (43.3)	0.32
b)	Females	24 (40)	34 (56.6)	
3.	Type 2 Diabetes duration	7.44±4.13	7.98±3.04	0.35
4.	BMI (kg/m ²)	24.61±4.46	25.60±4.42	0.37
5.	Weight (kg)	67.65±9.08	64.45±12.96	0.25
6.	Dyslipidemia	20 (33.3)	16 (26.6)	0.75
7.	Hypertension	30 (50)	26 (43.3)	0.77
8.	Family history	48 (80)	44 (73)	0.97
9.	FPG (mg/dl)	191.38±44.38	182.04±49.28	0.44
10.	Post-prandial glucose (mg/dl)	253.44±54.28	234.08±66.18	0.02
11.	HbA1c%	7.88±0.76	8.36±1.03	0.13

Table 1: Biochemical, clinical, and demographic data in study subjects